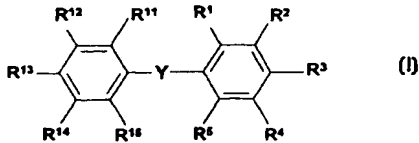


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(54) Title: SUBSTITUTED PHENYL DERIVATIVES, THEIR PREPARATION AND USE <div style="text-align: center;">  </div> <p style="text-align: right;">(I)</p>		
(57) Abstract The present invention discloses compounds having formula (I) wherein the substituents are defined in the application. The compounds are useful as chloride channel blockers.		



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Substituted phenyl derivatives, their preparation and use

The present invention relates to novel substituted phenyl derivatives which are potent chloride channel blockers and as such useful in the treatment of sickle cell anaemia,
5 brain oedema following ischaemia or tumours, diarrhea, hypertension (diuretic), bone metabolic disorders, osteoclast associated disorders and for the reduction of the intraocular pressure for the treatment of disorders such as glaucoma.

Background

10 Chloride channels serve a wide variety of specific cellular functions. Thus, chloride channels contribute to the normal function of skeletal and smooth muscle cells. Blockers of chloride channels are known to be useful in the treatment of brain oedema following ischaemia or tumours, diarrhea, hypertension (diuretic), sickle cell anaemia,
15 bone metabolic disorders, bone metastasizing cancers and in general osteoclast associated disorder as well as for the reduction of the intraocular pressure in disorders such as glaucoma. The compounds of the invention may also be useful in the treatment of allergic and inflammatory conditions and for the promotion of wound healing.

20 Sickle cell anaemia

The use of blockers of chloride channels for the treatment sickle-cell anaemia form a new therapeutic approach.

25 Sickle cell anaemia and the existence of sickle haemoglobin was the first genetic disease to be understood at the molecular level. The genetic defect underlying sickle cell anaemia causes the substitution of a single amino acid resulting in a mutant haemoglobin, sickle haemoglobin.

30 The physical manifestations of sickle cell disease is anaemia and painful ischaemic crises due to occlusion of the microcirculation by deformed erythrocytes (sickle cells). The primary cause of sickle erythrocyte deformation and distortion (or sickling) is a reversible polymerisation and gelation of sickle haemoglobin induced at the low oxygen tensions prevalent in metabolically active tissues. Sickle cells are also
35 characterised by an enhanced cation permeability, resulting in cation depletion and



cellular dehydration. Since the delay time for the polymerisation has been described as an extremely steep function of the sickle haemoglobin concentration itself, any decrease in cell volume will greatly increase the probability of sickling and thereby of vessel occlusion. Compounds which blocks the deoxygenation induced salt and
5 volume (water) loss may delay the sickling process enough to avoid occlusion upon the passage of the sickle erythrocyte through metabolically active tissue. It has been estimated that a delay time of only 10 sec may suffice.

Several membrane ion channels and transporters present in normal erythrocytes has
10 been suggested to participate in the altered membrane permeabilities of sickle cells. The favoured hypothesis has been stimulation of the Ca^{2+} -activated K^{+} -channel and several blockers of this channel has been suggested as therapeutic agents for the treatment of sickle-cell anaemia (Effects of Cetiedil on Monovalent Cation Permeability in the Erythrocyte: An explanation for the Efficacy of Cetiedil in the
15 treatment of Sickle Cell Anaemia, Berkowitz, L. R., Orringer, E. P., Blood cells, (283-288 (1982) and US patent No. 5.273.992).

Since, K^{+} efflux through a K-channel must be followed by an equal efflux of Cl^{-} to maintain electroneutrality, blockade of erythrocyte chloride channels should be as
20 effective as blocking the K-channels itself. An advantage to the use of chloride channel blockers is that salt loss which may occur due to activation of unknown K-channel types will indirectly be blocked too.

The compounds of the present invention are potent blockers of chloride channels as
25 measured by concomitant measurements of conductive netfluxes of chloride and membrane potentials in suspensions of erythrocytes, and the compounds are therefore predicted to be useful in the treatment of sickle-cell disease.

Osteoporosis and other osteoclast associated disorders.

30 The bone tissue is constantly renewed by the controlled activity of two cell types, osteoblasts, which lay down the new bone mass, and osteoclasts, which degrade and reabsorb the bone tissue by secretion of proteolytic enzymes such as cathepsin as well as acid, in particular HCl onto the bone surface. In osteoporosis the balance between the degradation and the synthesis is severely disturbed, which results in a
35 progressive loss of bone material and gradual weakening of the skeleton. Clinically,



hormone replacement studies has shown that the decline in estrogen levels at the onset of menopause is an important hormonal factor for the triggering of the disease. *In vitro* studies has shown that the osteoclasts are important targets cells for estrogen (i.e. Mano et al., Biochem. Biophys. Res. Commun. 223(3), 637-642, 1996) and that
5 the hormone inhibits the bone reabsorbing activity of osteoclasts via induction of osteoclast apoptosis (Kameda et al., J. Exp. Med., 186(4), 489-495, 1997) and/or via altered resorption capacity of the individual cells. Thus, the major estrogen effect on bone metabolism seems to be an inhibition of bone degradation by a direct effect on the osteoclasts.

10

Osteoclast physiology

As an alternative to hormone replacement down regulation of osteoclast acid producing activity by modulators of membrane transporters is an attractive, but hitherto clinical untested possibility. The physiological process whereby the osteoclast secrete
15 HCl - a key event in bone reabsorption - is relatively well understood and is conceptually similar to epithelial transport. Like epithelial cells osteoclasts are morphologically highly polarised cells with membrane transporters asymmetrically distributed between the bone-facing ruffled membrane and the smooth outer membrane. At the border between the ruffled and smooth membrane segments the
20 osteoclast is tightly attached to the bone surface, thus creating a sealed cavity between the cell and the bone surface. Pits are formed beneath the cavity as a result of HCl-induced demineralisation and enzymatic break-down of the bone matrix.

The ultimate event in the osteoclast HCl secretion across the ruffled membrane is an
25 active transport of H^+ by a vacuolar-type **proton pump** and a passive transport of Cl^- mediated via an outwardly rectifying **Cl-channel**. Due to HCl secretion the intracellular pH tend to increase and Cl^-_i tend to decrease, which - if allowed to occur - would quickly lead to cessation of acid secretion. Osteoclasts possess two important back-up systems aimed at maintaining a constant supply of intracellular H^+ and Cl^- for the
30 ruffled membrane transporters. First, the cell contains very high concentrations of the cytosolic enzyme **carbonic anhydrase II**, which catalyses the slow normally quite slow hydration of CO_2 to H_2CO_3 , a molecule which spontaneously dissociate to form H^+ and HCO_3^- . Second, the osteoclast outer membrane is packed with transporters (AE2), which mediate obligatory **Cl^-/HCO_3^- exchange**. Hence, HCO_3^- produced by the



carbonic anhydrase exzyme is exchanged with extracellular Cl^- . Apart from erythrocytes, osteoclasts are the mammalian cell type with the highest expression level of this protein.

- 5 In conclusion, the proton pump and the Cl^- -channel are fed by H^+ and Cl^- , respectively, via the concerted activity of the carbonic anhydrase and the anion exchanger.

Possible pharmacological intervention

- 10 In principle, any of the four proteins described above which are directly involved in the transcellular secretion of HCl are valid targets for interference with the resorptive properties of osteoclasts.

- Direct block of the proton pump is achievable with the antibiotic bafilomycin A1, which is an extremely potent, reversible inhibitor, whereas omeprazol - an irreversible inhibitor of the proton pump responsible for acid production in the stomach - is ineffective. *In vitro* bafilomycin A1 completely eliminates bone resorbtion in the bone slice assay pit formation test (Ohba et al, FEBS lett. 387(2-3), 175-178, 1996). *In vivo* the compound depresses bone degration in growing young rats (Keeling et al, Ann. N. Y. Acad. Sci., 834, 600-608 1997). The general applicability of the compound is limited due to its toxicity, which may be due to undesired inhibition of proton pumps in other areas of the body. Subtypes of the vacuolar proton pump exists, however it is not known if it will be possible to obtain pharmacological selectivity between these isoforms.

- 25 Inhibition of the carbonic anhydrase enzyme with acetazolamide is effective *in vitro* in the pit formation assay (Ohba et al, FEBS lett. 387(2-3), 175-178, 1996). Various inhibitors of the kidney carbonic anhydrase enzymes has previously been used as diuretic agents.
- 30 It is well established that osteoclast ability for bone resorbtion is highly correleated with the expression of the ruffled membrane Cl^- -channel (Schlesinger et. al. Jour. Biol. Chem., 272(30), 18636-18643, 1997). Block of the ruffled border Cl^- -channel is only achievable with very high concentratios of stilbene-sulfonates like DIDS, which makes firm conclusions about the efficacy of a selective block questionable, especially since



the stilbenes most likely will block the anion exchanger even better than the Cl⁻ channel.

A blockade of the anion exchanger in osteoclasts will also be a regulatory site for osteoclast activity optionally in combination with blockade of the chloride channel as a concomitant blockade of both channels or a blockade of either channel alone.

It is also well established that osteoclasts are involved in other bone-tissue related disorders (i.e. Clohisy et. al., J. Orthop. Res., 14(3), 396-702, 1996) and intervention with the osteoclast activity is very likely to prevent these types of disorders. The compounds of the present invention administered alone as well as in combination with other well known treatments of bone metabolism related diseases will have an effect on these diseases.

The compounds of the present invention are potent blockers of chloride channels and also the anion exchanger, as measured by concomitant measurements of conductive netfluxes of chloride and membrane potentials in suspensions of erythrocytes, and the compounds are therefore predicted to be useful in the treatment of sickle-cell disease, osteoporosis as well as other osteoclast associated disorders.

20

Prior art

Several chloride channel blockers and the use thereof have already been described:

Pflügers Arch (1986), 407 (suppl. 2), pages 128-141 describes several compounds with chloride channel blocking activity. A very potent compound described herein is 5-nitro-2-(3-phenylpropylamino)benzoic acid. The use of chloride channel blockers for the treatment of sickle cell anaemia is not disclosed herein.

US patent No. 4,889,612 describes Calixarene derivatives and their use as chloride channel blockers.

US patent No. 4,994,493 describes certain 5-nitrobenzoic acid derivatives and their use in the treatment of cerebral oedema.

35



WO 96/16647 describes the use of chloride channel blockers for reduction of the intraocular pressure and specifically the use of chloride channel blockers for the treatment of glaucoma.

- 5 WO 97/45400 describes other phenyl derivatives as chloride channels blockers;

The present invention relates to a series of substituted phenyl derivatives which are potent chloride channel blockers, and their use in the treatment of sickle-cell anaemia and osteoporosis as well as other bone metabolic disorders. The compounds of the present invention are novel and differs as well in the substitution patterns as in
10 pharmacodynamic properties such as kinetic behaviour, bioavailability, solubility and efficacy.

Objects of the Invention

- 15 It is an object of the present invention to provide novel substituted phenyl derivatives and pharmaceutically acceptable salts thereof which are useful in the treatment of disorders or diseases responsive to the blockade of chloride channels.

- 20 Still another object of the present invention is to provide a method of treating disorders or diseases responsive to the blockade of chloride channels, such as for example brain oedema following ischaemia or tumours, diarrhea, hypertension (diuretic), glaucoma and in particular sickle cell anaemia and osteoporosis.

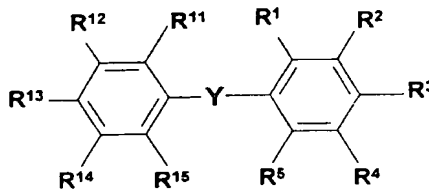
Summary of the Invention

25

The invention then comprises, inter alia, alone or in combination:

A compound having the formula

30



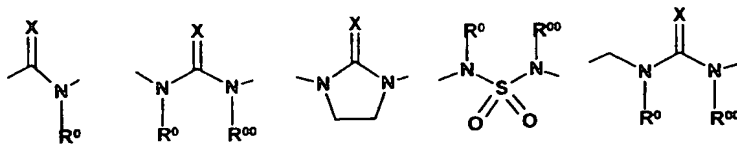
or a pharmaceutically acceptable salt thereof

wherein one of R^1 , R^2 and R^3 is a acidic functional group having a pKa value below 8 or a group which is convertible in vivo to such a group;

- 5 R^4 , R^5 and the other two substituents R^1 , R^2 and R^3 are each independently selected from hydrogen; alkyl; alkoxy; hydroxy; halogen; trifluoromethyl; cyano; nitro; amino; alkylamino, NHCOR^9 , CO_2R^9 , $-\text{CON}(\text{R}^9)_2$, $-\text{NHSO}_2\text{R}^9$, $-\text{SO}_2\text{N}(\text{R}^9)_2$ wherein R^9 represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl,
- 10 heteroaryl or R^9 comprises a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which can be substituted by alkyl or acyl; or $(\text{R}^9)_2$ together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom which can be substituted by alkyl or acyl; aryl, phenylamino, phenoxy or
- 15 heteroaryl wherein the phenyl, aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, hydroxy, alkoxy, halogen, trifluoromethyl, cyano, nitro, amino, NHCOR^9 , CO_2R^9 , $-\text{CON}(\text{R}^9)_2$, $-\text{NHSO}_2\text{R}^9$, $-\text{SO}_2\text{N}(\text{R}^9)_2$ wherein R^9 is as defined above; or R^3 and R^4 or R^4 and R^5 together form a 4-8 membered saturated or unsaturated ring and the other substituents R^1 , R^2 , R^3 , R^4 and R^5 is as defined above;

20

Y represents



wherein R^0 and R^{00} independently represents hydrogen or lower alkyl;

X represents O or S;

25

R^6 is hydrogen, or alkyl;

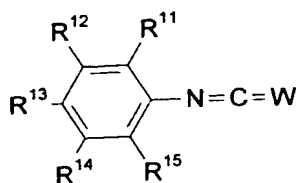
- R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen; alkyl; alkoxy; hydroxy; halogen; trifluoromethyl; cyano; nitro; amino; alkylamino; $-\text{COOR}^7$;
- 30 $-\text{NHSO}_2\text{-alkyl}$; $-\text{SO}_2\text{N}(\text{R}^7)_2$; $-\text{SO}_2\text{OR}^7$; $-\text{CO-R}^7$; aryl, phenylamino, phenoxy or heteroaryl wherein the phenyl, aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, hydroxy, alkoxy, halogen, trifluoromethyl, cyano, nitro,

amino and alkylamino, $-\text{COOR}^7$; $\text{CON}(\text{R}^7)_2$; $-\text{NH}\text{SO}_2\text{R}^7$; $-\text{SO}_2\text{N}(\text{R}^7)_2$; $-\text{SO}_2\text{OR}^7$; $-\text{CO-R}^7$,
 or one of R^{11} and R^{12} , R^{12} and R^{13} , R^{13} and R^{14} and R^{14} and R^{15} together form a 4-8
 membered saturated or unsaturated ring and the other substituents R^{11} , R^{12} , R^{13} , R^{14}
 and R^{15} is as defined above and wherein R^7 represents hydrogen, alkyl, cycloalkyl,
 5 cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl or R^7 comprises a 5-8 membered
 ring optionally containing double bonds and optionally containing one or two
 heteroatoms which can be substituted by alkyl or acyl; or $(\text{R}^7)_2$ together with the
 heteroatom to which it is connected represents a 5-8 membered ring optionally
 containing double bonds and optionally containing another heteroatom which can be
 10 substituted by alkyl or acyl;

a method for the preparation of a compound as above, comprising:

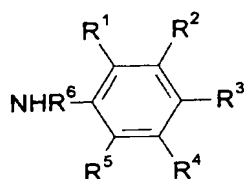
a) reacting a compound having the formula

15



wherein W is O , or S and R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above, with a
 compound having the formula

20



wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 is as defined above, or

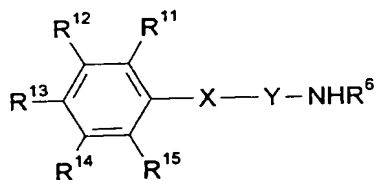
25 b) reacting a compound having the formula



WO 00/24707

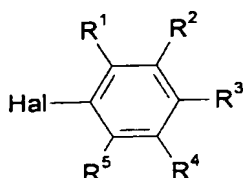
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9



wherein X, Y, R⁶, R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ is as defined above, with a compound having the formula

5



wherein Hal is halogen and R¹, R², R³, R⁴ and R⁵ is as defined above,

10 whereafter optionally the compound obtained is converted to another compound of the invention and/or a pharmaceutically acceptable salt thereof is formed using conventional methods;

a chloride channel blocker as above optionally combined with known therapeutic
15 treatment of bone metabolic disorders;

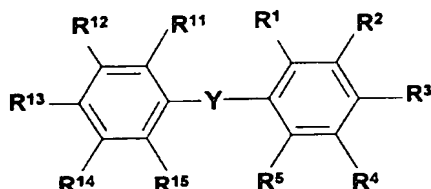
a pharmaceutical composition comprising a therapeutically effective amount of a compound as any above or a pharmaceutically acceptable salt thereof together with at least one pharmaceutically acceptable carrier or diluent;

20 the use of a compound as above for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels;

25 a method for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels, comprising administering to such a living animal body in need thereof a therapeutically effective amount of a compound as above;

Detailed disclosure of the invention

The invention comprises in a preferred aspect a compound of the formula



wherein one of R¹, R² and R³ is

3-hydroxy-4-oxo-pyranyl, 2-hydroxy-4-oxo-pyrimidyl, 3,5-dioxo-1,2,4-oxadiazolidinyl,
 2,4-dioxo-imidazolidinyl, 2,5-dioxo-3-hydroxy-pyrrolyl, 2,5-dioxo-pyrrolidinyl, 2,4-dioxo-
 10 1,3-thiazolidinyl, 3-hydroxy-isoxazolyl, 5-hydroxy-isoxazolyl, 3-hydroxy-isothiazolyl, 3-
 hydroxy-1,2,5-thiadiazolyl, tetrazolyl, 3-hydroxy-triazolyl, 3-hydroxy-pyrazolyl, 2-
 hydroxy-1,3,4-oxadiazolyl or 2-hydroxy-3,4-dioxo-cyclobutenyl, NH₂, -COOR¹⁶,
 -CH₂COOR¹⁶, -CON(R¹⁶)₂, -NHSO₂-R¹⁶, -SO₂N(R¹⁶)₂, -SO₂OR¹⁶, -PO₃H₂, -PO₃RH,
 -PO₂NH₂, -CONHOH, -CONHCN, -CONHSO₂R¹⁶ and -CONHNH₂, wherein R¹⁶ is
 15 hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl or
 R¹⁶ comprises a 5-8 membered ring optionally containing double bonds and optionally
 containing one or two heteroatoms, or (R¹⁶)₂ together with the heteroatom to which it
 is connected represents a 5-8 membered ring optionally containing double bonds and
 optionally containing another heteroatom; and the other of R¹, R² and R³ is as defined
 20 above;

A preferred aspect of the invention comprises compound as above, wherein one of R¹,
 R² and R³ represents COOH, CH₂COOR¹⁶, CON(R¹⁶)₂, tetrazolyl, methyltetrazolyl,
 NHSO₂R¹⁶, CO₂R¹⁶, CO₂N(R¹⁶)₂, SO₂N(R¹⁶)₂, CONHSO₂R¹⁶, SO₂OR¹⁶, wherein R₁₆ is
 25 as defined above;

Another preferred aspect of the invention comprises a compound as above wherein
 R⁴, R⁵ and the remaining of R¹, R² or R³ independently represents hydrogen, alkyl,
 nitro, amino, alkylamino, CO₂R⁹, CF₃, alkyl, halogen, hydroxy, alkoxy, NHCOR⁹,
 30 -CON(R⁹)₂, aryl optionally substituted with CON(R⁹)₂, NHCOR⁹, SO₂N(R⁹)₂, CO₂R⁹,
 wherein R⁹ is as defined above;



Yet another preferred aspect of the invention comprises a compound as above wherein one or more of R^{11} , R^{12} , R^{13} , R^{14} and R^{15} independently represents CF_3 , halogen, $COOH$, CH_2COOR^{16} , $CON(R^{16})_2$, $NHSO_2R^{16}$, CO_2R^{16} , $CO_2N(R^{16})_2$,
5 $SO_2N(R^{16})_2$, $CONHSO_2R^{16}$, SO_2OR^{16} or aryl optionally substituted with $NHCOR^7$, CO_2R^7 , $-CON(R^7)_2$, $-NHSO_2R^7$, $-SO_2N(R^7)_2$ wherein R^7 is as defined above; or R^{11} and R^{12} together with the phenyl group to which they are attached forms a 6-membered unsaturated ring; R^{16} and R^7 is as defined above;

10 Y preferentially represents $-NHCONH-$;

In a preferred aspect of the invention

Y represents $-NHCONH-$; R^1 represents tetrazolyl, and R^3 represents halogen, in particular Bromo; or R^3 represents phenyl which is substituted by $SO_2N(R^{16})_2$ wherein
15 R^{16} is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl or R^{16} comprises a 5-8 membered ring optionally containing double bonds and optionally containing one heteroatom, or $(R^{16})_2$ together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom which can be substituted by alkyl or acyl;

20

In yet another preferred aspect of the invention Y represents $-NHCONH-$; R^{12} represents CF_3 , or halogen, in particular bromo or chloro; R^{13} represents hydrogen or halogen in particular chloro; and R^{14} represents hydrogen or CF_3 ;

25 The most preferred aspect of the invention comprises the following compounds:

N-phenyl-N'-(2-carboxyphenyl) urea;

N-(3-trifluoromethylphenyl)-N'-(2-carboxyphenyl)-N-methyl urea;

N-(3-trifluoromethylphenyl)-N'-(4-bromo-2-carboxyphenyl) urea;

N-(3-trifluoromethylphenyl)-N'-(2-carboxy-4-chlorophenyl) urea;

30 N-(3-trifluoromethylphenyl)-N'-(2-carboxy-4-fluorophenyl) urea;

N-(3-bromophenyl)-N'-(2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-trifluoromethylphenyl)-N'-(4'-(N,N-dimethylsulfamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;

35 N-(3-bromophenyl)-N'-(4'-(N,N-dimethylsulfamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;



- N-(3-bromophenyl)-N'-(4'-(N,N-dimethylcarbamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4-amino-2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4-acetylamino-2-(1-H-tetrazol-5-yl)phenyl) urea;
- 5 N-(3-trifluoromethylphenyl)-N'-(4'-carbamoyl-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4'-(N,N-dimethylcarbamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4'-carboxy-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4'-(N-phenylcarbamoyl)-2-(5-tetrazoyl)-4-biphenyl)
- 10 urea;
- N-(2-indan)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(4-biphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-biphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-acetylphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea;
- 15 N-(3-trifluoromethylphenyl)-N'-(2-(1-methyltetrazol-5-yl)-4-biphenyl) urea;
- N-(3-biphenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-(3-pyridyl)phenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea hydrochloride;
- N-(3-bromophenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-bromophenyl)-N'-(3'-nitro-2-(1-H-tetrazol-5-yl)-biphenyl) urea;
- 20 N-(3-bromophenyl)-N'-[4'-(sulfoamido-N-methylpiperazinium chloride)-2-(1-H-tetrazol-5-yl)-4-biphenyl]urea;
- N-(3-bromophenyl)-N'-[4'-carbamoyl-N-methylpiperazine)-2-(1-H-tetrazol-5-yl)-4'-biphenyl] urea;
- N-(3,5-dichlorophenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea;
- 25 N-(4-trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(4-bromophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(3-methoxyphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(3-chlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(3-methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- 30 N-(3,4-dichlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(2-naphthyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(4-methyl-3-nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(2-chloro-4-trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;



- N-(3,5-di(trifluoromethyl)phenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(3,5-dimethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-ethoxyphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-methoxyphenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea;
5 N-(2-trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-bromophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-chlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-fluorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-chloro-3-trifluoromethylphenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea;
10 N-(3-bromophenyl)-N'-(2,3-difluorophenyl) urea;
N-(2-methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-ethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
15 N-(3-fluorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-yl)phenyl] urea;
N-(4-[2-propyl]phenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(3-nitrophenyl)-N'-[4-bromo-2-(5-tetrazol-5-yl)phenyl] urea;
N-(3-acetylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
20 and pharmaceutically acceptable addition salts of any of the compounds above;

- Examples of pharmaceutically acceptable addition salts of the compounds of the invention include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulfate, citrate, lactate, tartrate,
25 maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate, methanesulfonate, stearate, succinate, glutamate, glycollate, toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate and the acetate. Such salts are formed by procedures well known in the art.
- 30 Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.



Definition of substituents

Halogen is fluorine, chlorine, bromine or iodine.

- 5 Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

10

Amino is NH_2 or NH-alkyl or N-(alkyl)₂, wherein alkyl is as defined above.

Acyl is -CO-alkyl wherein alkyl is as defined above.

- 15 Aryl is an aromatic hydrocarbon such as phenyl and naphthyl;

The acidic functional group having a pKa below 8 or a group which is converted in vivo to such group are groups such as 3-hydroxy-4-oxo-pyranyl, 2-hydroxy-4-oxo-pyrimidyl, 3,5-dioxo-1,2,4-oxadiazolidinyl, 2,4-dioxo-imidazolidinyl, 2,5-dioxo-3-hydroxy-pyrrolyl, 20 2,5-dioxo-pyrrolidinyl, 2,4-dioxo-1,3-thiazolidinyl, 3-hydroxy-isoxazolyl, 5-hydroxy-isoxazolyl, 3-hydroxy-isothiazolyl, 3-hydroxy-1,2,5-thiadiazolyl, tetrazolyl, 3-hydroxy-triazolyl, 3-hydroxy-pyrazolyl, 2-hydroxy-1,3,4-oxadiazolyl and 2-hydroxy-3,4-dioxo-cyclobutenyl, NH_2 , $-\text{COOR}^{16}$, $-\text{CH}_2\text{COOR}^{16}$, $-\text{CON}(\text{R}^{16})_2$, $-\text{NHSO}_2\text{R}^{16}$, $-\text{SO}_2\text{N}(\text{R}^{16})_2$, $-\text{SO}_2\text{OR}^{16}$, $-\text{PO}_3\text{H}_2$, $-\text{PO}_3\text{RH}$, $-\text{PO}_2\text{NH}_2$, $-\text{CONHOH}$, $-\text{CONHCN}$, $-\text{CONHSO}_2\text{R}^{16}$ and 25 $-\text{CONHNH}_2$, wherein R^{16} is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl or aralkyl, heteroaryl or R^{16} comprises a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, or R^{16} together with the heteroatom to which it is connected form a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom;

30

Heteroaryl is a 5- or 6-membered heterocyclic monocyclic group. Such a monocyclic heteroaryl group includes, for example, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl,



2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl.

- 5 A 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms includes for example pyrrolidine, piperidine, piperazine, morpholine, cyclohexyl, cyclohexen, dihydropyrrole, dihydrofuran, dihydrothiophen, dihydropyridine, dihydropyridazine, dihydropyrimidine, dihydropyrazine, tetrahydropyridine, tetrahydropyridazine, tetrahydropyrimidine, tetrahydropyrazine,
- 10 homopiperazine, homopiperidine, azacyclooctane.

The compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the

15 purposes of this invention.

Steric isomers

It will be appreciated by those skilled in the art that the compounds of the present

20 invention contain several chiral centres and that such compounds exist in the form of isomers (i.e. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Some of the compounds of the present invention exist in (+) and (-) forms as well as in

25 racemic forms. Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the

30 present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+)

35 or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the



formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like.

Additional methods for the resolution of optical isomers, known to those skilled in the art may be used, and will be apparent to the average worker skilled in the art. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Method of preparation

The compounds of the invention may be prepared in numerous ways. The compounds of the invention and their pharmaceutically acceptable derivatives may thus be prepared by any method as described above or known in the art for the preparation of compounds of analogous structure, and as shown in the representative examples which follow.

Biology

The compounds of the present invention are potent blockers of chloride channels in normal as well as sickle cell erythrocytes. The ability of the compounds to block the erythrocyte chloride channels can not be demonstrated by classical electrophysiological measurements such as patch clamping, since the channel unit conductance is below the detection limit of these techniques.

All dose-response experiments were therefore performed by concomitant measurements of conductive netfluxes of Cl^- (J_{Cl}) and membrane potentials (V_m) in suspensions of erythrocytes (Bennekou, P. and Christophersen, P. (1986), Flux ratio of Valinomycin - Mediated K^+ Fluxes across the Human Red Cell Membrane in the presence of the Protonophore CCCP. J. Membrane Biol. 93, 221-227.).

The membrane Cl^- conductances (G_{Cl}) were calculated by the following equation (Hodgkin, A. L. and Huxley, A.F. (1952) The components of membrane conductance in the giant axon of Loligo. J. Physiol. Lond. 116, 449-472):

$$G_{\text{Cl}} = \frac{F \cdot J_{\text{Cl}}}{(V_m - E_{\text{Cl}})}$$



where F is the Faraday constant, E_{Cl} is the Nernst potential for the Cl^- -ion.

Administration of 3-Trifluoromethylphenyl-2-carboxyphenyl urea to a suspension of normal erythrocytes blocked G_{Cl} more than 95 % with a K_D -value of 1.3 μM . The compound equipotently blocked G_{Cl} from oxygenated as well as deoxygenated
5 homozygoteous sickle cell erythrocytes.

The K_D -value for for N-(3-Trifluoromethylphenyl)-N'-(4'-(N,N-dimethylsulfamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea in this test was 0.3 μM .

- 10 The compounds of the present invention are useful as blockers of the bone degrading activity of osteoclasts. For measuring the activity of the compounds different osteoclast inhibition assays known in the art can be used.

Pharmaceutical compositions

- 15 While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. Optionally the compounds of the invention can be administered together with another therapeutic compound. This can optionally be in
20 the form of a pharmaceutical composition containing more than one compound.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and,
25 optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical
30 (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or
35 diluent, may thus be placed into the form of pharmaceutical compositions and unit



WO 00/24707



PCT/DK99/00575

dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including
5 subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of
10 active ingredient or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the
15 following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form
20 preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

25 In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

30

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and
35 the like. The term "preparation" is intended to include the formulation of the active



compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral
5 administration.

For preparing suppositories, a low melting wax, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then
10 poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

15 Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

20 The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or
25 aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

30 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely
35 divided active component in water with viscous material, such as natural or synthetic



WO 00/24707



PCT/DK99/00575

gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly
5 before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

10 For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more
15 emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth;
20 pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional
25 means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

30 Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon



dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Methods of treating

The compounds of the present invention are very useful in the treatment of sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhea, hypertension (diuretic), bone metabolic disorders, osteoclast associated disorders and glaucoma, due to their potent chloride channel blocking activity. These properties make the compounds of this invention extremely useful in the treatment of sickle cell anaemia,



brain oedema following ischaemia or tumors, diarrhea, hypertension (diuretic), bone metabolic disorders, osteoclast associated disorders and glaucoma, as well as other disorders sensitive to the chloride channel blocking activity of the compounds of the present invention. The compounds of this invention may accordingly be administered
5 to a living animal body, including a human, in need of treatment, alleviation, or elimination of an indication associated with or responsive to chloride channel blocking activity. This includes especially sickle cell anaemia, brain oedema following ischaemia, or tumors, diarrhea, hypertension (diuretic), bone metabolic disorders, osteoclast associated disorders and glaucoma.

10 Suitable dosage range are 0.1-500 milligrams daily, and especially 10-70 milligrams daily, administered once or twice a day, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject
15 involved, and further the preference and experience of the physician or veterinarian in charge. When administered in combination with compounds known in the art for treatment of the diseases, the dosis regimen may be reduced.

The invention then comprises alone or in combination, the following:

- 20 the use of any of the compounds as mentioned above for the preparation of a medicament for the treatment of sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhea, hypertension (diuretic), bone metabolism disorders, glaucoma, allergic or inflammatory conditions or healing ulcers;
- 25 the use of any of the compounds as above combined with the use of other bone metabolism controlling compounds for the treatment of bone metabolic disorders or conditions.
- 30 the use as above wherein the known compounds are bisphosphonates such as etidronate, pamidronate, or clodronate optionally combined with calcium; oestrogen-receptor active compounds such as oestrogen i.e. oestradiol and ethyloestradiol, calcitonin, 1,25-dihydroxyvitamine D and metabolites thereof, fluoride, growth hormone, parathyreoidea hormone, triodo-thyrosine, protease inhibitors ie. collagen
35 degrading enzymes, or cancer therapeutic agents.



a method for the treatment of a disorder or disease of a living animal body which disorder or disease is sickle-cell anaemia, brain oedema following ischaemia or tumours, diarrhea, hypertension (diuretic), bone metabolic disorders, glaucoma,
5 allergic or inflammatory conditions or ulcers, comprising administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound as any above;

a method for the treatment of a disorder or disease of a living animal body which
10 disorder or disease is a bone metabolic disorder comprising administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound as any above optionally in combination with other bone metabolism controlling compounds.

15 In the context of this invention a bone metabolic disorder or disease covers any deviation in the bone formation and/or bone resorption as ie. osteoclast associated diseases or disorders, age related decrease in bone mass, osteoporosis, osteopeni, osteogenesis imperfecta, osteopetrosis, osteosklerosis, Paget's disease of bone, bone metastasizing cancers, osteomyelitis, osteonekrosis, fluorosis, bone malignancies etc.
20 and covers in general all clinical types of the mentioned diseases;

In the context of this invention the compounds known for treatment for bone metabolic disorders includes bisphosphonates such as etidronate, pamidronate, oestrogen-receptor binding compounds such as oestrogen i.e. oestradiol and ethyloestradiol;
25 calcitonin, 1,25-dihydroxyvitamine D and metabolites thereof, fluoride, growth hormone, parathyroid hormone, triiodo-thyrosine, cancer therapeutic agents and inhibitors of collagen degrading enzymes such as protease inhibitors.

In the context of this invention the method of treatment of a disorder or disease of a
30 living animal body including a human comprising administering a compound of the invention optionally together with a known compound and optionally administerering the compound(s) in a reduced dosis;

The treatment of the diseases and disorder can be in chronical or a long term
35 treatment as well as a treatment of sudden crisis in the disease and disorder.



WO 00/24707



PCT/DK99/00575

The following examples will illustrate the invention further, however, they are not to be construed as limiting.

5

Example 1**N-3-Trifluoromethylphenyl-N'-(2-carboxyphenyl) urea**

3-Trifluoromethylphenyl isocyanate (1.87g, 10 mmol) and 2-aminobenzoic acid (1.37g, 10 mmol) were in toluene (50 mL) was stirred until the 2-aminobenzoic acid had been consumed. The product was filtered off. M.p. 171-172 °C.

10

The following compounds were prepared analogously:

N-Phenyl-N'-(2-carboxyphenyl) urea. Mp. 168-169°C.

N-(3-Trifluoromethylphenyl)-N'-(2-carboxyphenyl)-N-methyl urea. Mp. 113-116 °C.

N-(Trifluoromethylphenyl)-N'-(4-bromo-2-carboxyphenyl) urea. Mp. 177-178°C.

15 N-(Trifluoromethylphenyl)-N'-(2-carboxy-4-chlorophenyl) urea. Mp. 167-168°C.

N-(Trifluoromethylphenyl)-N'-(2-carboxy-4-fluorophenyl) urea. Mp. 176°C

N-(3-Bromophenyl)-N'-(2-(1-H-tetrazol-5-yl)-4-biphenyl) urea. Mp. >240 °C.

N-(3-Trifluoromethylphenyl)-N'-(4'-(N,N-dimethylsulfamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea. Mp. 258-260 °C.

20 N-(3-Bromophenyl)-N'-(4'-(N,N-dimethylsulfamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea. Mp. 242-244 °C.

N-(3-Bromophenyl)-N'-(4'-(N,N-dimethylcarbamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea. Mp. 173-175 °C.

N-(3-Trifluoromethylphenyl)-N'-(4-amino-2-(1-H-tetrazol-5-yl)phenyl) urea. Mp. 175-

25 180 °C.

N-(3-Trifluoromethylphenyl)-N'-(4-acetylamino-2-(1-H-tetrazol-5-yl)phenyl) urea. Mp. 280-282 °C.

N-(3-Trifluoromethylphenyl)-N'-(4'-carbamoyl-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea. Mp. 252-253 °C.

30 N-(3-Trifluoromethylphenyl)-N'-(4'-(N,N-dimethylcarbamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea. Mp. 263-263 °C.

N-(3-Trifluoromethylphenyl)-N'-(4'-carboxy-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea. Mp. >300 °C.



- N-(3-Trifluoromethylphenyl)-N'-(4'-(N-phenylcarbamoyl)-2-(1H-tetrazol-5-yl)-4-biphenyl) urea. Mp. >300 °C.
- N-(2-Indan)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea. Mp. 154-157 °C.
- N-(4-Biphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea. Mp. 224-226 °C.
- 5 N-(3-Biphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea. Mp. 189-191 °C.
- N-(3-Acetylphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea. Mp. 115-120°C.
- N-(3-Trifluoromethylphenyl)-N'-(2-(1-methyltetrazol-5-yl)-4-biphenyl) urea. Mp. 170-171°C.
- N-(3-Biphenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea. Mp. 232-234 °C.
- 10 N-(3-(3-Pyridyl)phenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea hydrochloride. Mp. 211-213 °C.
- N-(3-Bromophenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea. Mp. >275 °C.
- N-(3-Bromophenyl)-N'-[3'-nitro-2-(1-H-tetrazol-5-yl)biphenyl] urea. Mp. 266-268°C.
- N-(3-Bromophenyl)-N'-[4'-(sulfoamido-N-methylpiperazinium chloride)-2-(1-H-tetrazol-15 5-yl)-4-biphenyl] urea. Mp. 176-177°C.
- N-(3-Bromophenyl)-N'-[4'-carbamoyl-N-methylpiperazine)-2-(1-H-tetrazol-5-yl)-4-biphenyl] urea. Mp. 155-158°C.
- N-(3,5-Dichlorophenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea. Mp. 246-255°C.
- N-(4-Trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 263-20 264°C.
- N-(4-Bromophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 242-243°C.
- N-(3-Methoxyphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 180-200°C.
- N-(3-Chlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 254-256°C.
- N-(3-Methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 258-263°C.
- 25 N-(3,4-Dichlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 228-231°C.
- N-(2-Naphthyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 230°C. (decomp.)
- N-(4-Methyl-3-nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 231-234°C.
- N-(2-Chloro-4-trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. 30 Mp. 269-271°C.
- N-(3,5-Di(trifluoromethyl)phenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 268-271°C.



- N-(3,5-Dimethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 258-268°C.
N-(4-Ethoxyphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 168-170°C
N-(4-Methoxyphenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea. Mp. 215-218°C.
N-(2-Trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 268-
5 270°C.
N-(2-Bromophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea Mp. 277-279°C.
N-(2-Chlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 270-273°C.
N-(2-Fluorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 270-273°C.
N-(4-Chloro-3-trifluoromethylphenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea
10 Mp.259-261°C.
N-(3-Bromophenyl)-N'-(2,3-difluorophenyl) urea. Mp. 210-220°C
N-(2-Methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 261-264°C.
N-(2-Ethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 272-273°C.
N-(4-Methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 253-254°C.
15 N-(2-Nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 270-272°C.
N-(3-Fluorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-yl)phenyl] urea. Mp. 269-271°C.
N-(4-[2-Propyl]phenyl)-N'-[4-bromo-2-(1-H-tetrazol-5yl)phenyl] urea. Mp. 233-237°C.
N-(3-Nitrophenyl)-N'-[4-bromo-2-(5-tetrazol-5-yl)phenyl] urea. Mp. 225-230°C.
N-(3-Acetylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. >300°C.
20 N-(4-Nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea. Mp. 230-235°C.

Example 2

(intermediate)

25

2-Chloro-5-hydroxybenzoic acid

5-Amino-2-chlorobenzoic acid (85%, 10g, 49.7 mmol) was suspended in diluted sulphuric acid (1.25%, 800 mL) and cooled to 5 °C on an ice bath. Sodium nitrite (5g, 72 mmol) dissolved in water (150 mL) was added slowly while keeping the
30 temperature of the reaction below 5 °C. After addition of the sodium nitrite the reaction was stirred for another 45 min at 5-10 °C until a clear solution was obtained. The reaction mixture was poured into hot (70-85 °C) water (1.5 L), charcoal added and the reaction mixture heated at reflux for 25 min. Filtration and extraction with ethyl acetate afforded 6.7g of the desired product as light brown crystals

**Example 3**

(intermediate)

2-Chloro-3-hydroxy-4-nitro-benzoic acid

5 To a solution of 2-chloro-5-hydroxybenzoic acid (6.5g, 38 mmol) in cold acetic acid (150 mL) was added concentrated nitric acid (2.7 mL, 38 mmol). After addition the reaction mixture was stirred for 30 min at room temperature then heated at 35 °C for 20 min. The reaction mixture was poured into ice and the product filtered off to give
10 1.5 g of the desired compound as yellow crystals.

Example 4

(intermediate)

4-Amino-6-chloro-3-hydroxybenzoic acid

15 2-Chloro-3-hydroxy-4-nitro-benzoic acid (2.2g, 10 mmol) dissolved in ethanol (120 mL) was reduced over Raney-Ni to give 1.7 g of black crystals.

20

Example 5

(intermediate)

5-(2-Aminophenyl)-1-H-tetrazole

25 2-Aminobenzonitrile (9.44 g, 80 mmol), sodium azide, (6.24 g, 0.1 mol), ammonium chloride (5.12 g, 0.1 mol) and dimethylformamide (50 mL) were mixed and heated at 120 °C overnight. The solvent was evaporated and the residue taken up in water. The crude product was isolated by filtration and re-crystallised from water. A yield of 8.4 g of pure product was obtained

30

Analogously were made:

5-(2-Amino-5-bromophenyl)-1-H-tetrazole

5-(4-Amino-3-biphenyl)-1-H-tetrazole

35 5-(2-Amino-5-nitrophenyl)-1-H-tetrazole

5-(2-Amino-5-(2-naphthyl)phenyl)-1-H-tetrazole

5-(2-Amino-5-(3-pyridyl)phenyl)-1-H-tetrazole

5-(2-Amino-5-(1-naphthyl)phenyl)-1-H-tetrazole



- 5-(2-Amino-5-(4-trifluoromethylphenyl)phenyl)-1-H-tetrazole
5-(2-Amino-5-(3-furyl)phenyl)-1-H-tetrazole
5-(2-Amino-5-(3-thienyl)phenyl)-1-H-tetrazole
5-(2-Amino-5-(4-trifluoromethylphenyl)phenyl)-1-H-tetrazole
5 5-(2-Amino-5-(3-nitrophenyl)phenyl)-1-H-tetrazole
5-(2-Amino-5-(4-ethoxycarbonylphenyl)phenyl)-1-H-tetrazole
5-(2-Amino-5-(4-diethylaminocarbonylphenyl)phenyl)-1-H-tetrazole
5-(2-Amino-5-(4-aminocarbonylphenyl)phenyl)-1-H-tetrazole
5-[2-Amino-5-(4-{sulfoamido-N'-methylpiperazine}phenyl)phenyl]-1-H-tetrazole
10 5-[2-Amino-5-(4-{carbamoyl-N'-methylpiperazine}phenyl)phenyl]-1-H-tetrazole

Example 6

(intermediate)

15

2-Methylsulfonamidocarbonylaniline

- Lithium methanesulfonamidate (1.0 g, 10 mmol) and isatoic anhydride (1.63 g, 10 mmol) in dimethyl sulfoxide (5 mL) were heated at 80 °C for 30 min. The reaction was cooled down to room temperature and acidified with hydrogen chloride in diethyl ether.
20 The ether was evaporated and water added. The precipitated oil was purified by column chromatography on silica gel eluting with ethyl acetate/methanol (95:5). The desired material was obtained in a yield of 0.52 g.

Analogously were made;

25

2-phenylsulfonamidocarbonylaniline

Example 7

(intermediate)

30

Ethyl N-(2-bromoethyl)aminobenzoate

- Dibromomethane (21.5 mL, 0.25 mol), ethyl-2-aminobenzoate (3.7 mL, 0.25 mmol) and triethylamine (4.2 mL, 30 mmol) were mixed in dimethylformamide (50 mL) and
35 heated at 110°C for five hours. After cooling to room temperature the reaction was poured onto ice and extracted with diethyl ether. The organic solution was washed with water, dried over magnesium sulphate and evaporated to dryness. The residue was



purified by column chromatography on silica gel using dichloromethane as eluent to give 3.3 g of the desired material.

Example 8

5

1-(3-Trifluoromethylphenyl)-3-(2-carboxyphenyl)-2-imidazolidone

To a solution of N-(3-trifluoromethylphenyl)-N'-(2-ethoxycarbonylphenyl)-1,2-diaminoethane (1.1 g, 3.1 mmol) and triethylamine (1.1 mL, 7.5 mmol) in toluene was added phosgene in toluene (1.84 mL, 3.5 mmol). After stirring at room temperature for 30 min. Water and diethyl ether were added. The organic phase was dried and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel using dichloromethane as eluent. The isolated ester (0.96 g) was hydrolysed in 4N aqueous sodium hydroxide to give the desired compound in a yield of 0.6 g. M.p. 197-198 °C.

15

Example 9

(intermediate)

20

2-Amino-4-phenylbenzonitrile

A mixture of 2-amino-5-bromobenzonitrile (1.0 g, 5 mmol), phenylboronic acid (0.92 g, 7.5 mmol), tetrakis(triphenylphosphine)palladium (50 mg) and potassium carbonate (3.5 g, 25 mmol) in dimethoxyethane/water 2:1 (60 mL) was heated at reflux for 4 hours. After cooling to room temperature the reaction was diluted with water and extracted with ethyl acetate. The organic phase was dried and solvent evaporated. Trituation with petroleum ether gave 0.89 g of the desired compound.

25

Similarly was made;

2-Amino-5-(2-naphthyl)benzonitrile

30 2-Amino-5-(3-pyridyl)benzonitrile

2-Amino-5-(1-naphthyl)benzonitrile

2-Amino-5-(4-trifluoromethylphenyl)benzonitrile

2-Amino-5-(3-furyl)benzonitrile

2-Amino-5-(3-thienyl)benzonitrile

35 2-Amino-5-(3-nitrophenyl)benzonitrile

2-Amino-5-(4-ethoxycarbonylphenyl)benzonitrile



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30

- 2-Amino-5-(4-diethylaminocarbonylphenyl)benzonitrile
2-Amino-5-(4-aminocarbonylphenyl)benzonitrile
1-(3-nitro-4-biphenyl)-1,2-dihydro-1,2,4-triazol-3-one
2-Amino-5-(4-[sulfamido-N'-methylpiperazine]phenyl)benzonitrile
5 2-Amino-5-(4-[carbamoyl-N'-methylpiperazine]phenyl)benzonitrile

Example 10

4-Methylphenylboronic acid

- 10 To a solution of 4-iodotoluene (35g, 160.5 mmol) in diethyl ether (400 mL) was added n-butyllithium (2 M in pentane, 88.3 mL, 176.6 mmol) at 0 °C. After stirring at 0 °C for another 15 min the solution was cooled to -60 °C and tributylborate (60.6 mL, 224.7 mmol) was added. The cooling bath was removed and the reaction allowed to heat up
15 to room temperature. The solution was acidified with hydrochloric acid (2 N, 280 mL) and the organic phase separated off. The aqueous phase was extracted with diethyl ether 2 x 125 mL). The combined organic phases were extracted with sodium hydroxide (1 N, 5 x 50 mL). The combined aqueous extracts were acidified to give 18.6g of the desired material.

20

Example 11

4-Carboxyphenylboronic acid

- 25 To a solution of 4-methylphenylboronic acid (34g, 0.25 mol) in aqueous sodium hydroxide (0.5 N, 1000 mL) was added potassium permanganate (83g, 0.53 mol) while keeping the temperature at 35-40 °C. After the addition the reaction was filtered and the filtrate acidified with concentrated hydrochloric acid (65 mL). The product was filtered off. A yield of 29.6 g was obtained. M.p. 228 °C.

30

Example 12

4-Ethoxycarbonylphenylboronic acid

- 35 A solution of 4-carboxyphenylboronic acid (15g, 0.09 mol), 99% ethanol (150 mL) and concentrated sulphuric acid (0.5 mL) was heated to reflux for two days. The volume was reduced to approximately 20 mL. The residue was triturated with petroleum ether to give 13.4 g of the desired material.



Example 13

4-Aminocarbonylphenylboronic acid

5 A solution of 4-carboxyphenylboronic acid (10g, 0.06 mol) and thionyl chloride 875 mL) was heated to 50-60 °C overnight. The thionyl chloride was evaporated off. Half of the residue was added to concentrated ammonia (30 mL). The reaction was heated to reflux. Hot filtration and subsequent acidification of the filtrate yielded the crude
10 material. The crude material was purified by suspending it in diluted sodium hydrogencarbonate to give 1.09 of the desired material.

Similarly was made;

4-Dimethylaminocarbonylphenylboronic acid

15

Example 14

4-Biphenyl-2-(1-H-tetrazol-5-yl)phenyl urea

20 To a solution of N,N-carbonyldiimidazole (0.96g, 5.0 mmol) and imidazole (0.68g, 10 mmol) in tetrahydrofuran (10 mL) at 0 °C was added 4-aminobiphenyl (1.0g, 5.9 mmol) in tetrahydrofuran (10 mL). After stirring at 0 °C for 10 min 5-(2-aminophenyl)tetrazole (1.14g, 7.1 mmol) was added. The reaction was stirred for another 4 hours and filtered. The filtrate was evaporated to dryness and the crude product purified by
25 column chromatography. A yield of 0.28g was obtained. M.p. 224-226 °C.

Similarly was made;

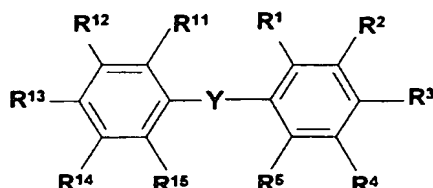
3-biphenyl-2-(1-H-tetrazol-5-yl)phenyl urea. M.p. 189-191 °C.

30 5-indanyl-2-(1-H-tetrazol-5-yl)phenyl urea. M.p. 154-157 °C.



CLAIMS:

1. A compound having the formula



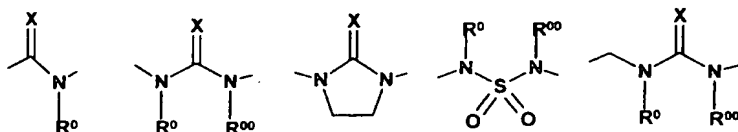
5

or a pharmaceutically acceptable salt thereof

wherein one of R^1 , R^2 and R^3 is a acidic functional group having a pKa value below 8
10 or a group which is convertible in vivo to such a group;

R^4 , R^5 and the other two substituents R^1 , R^2 and R^3 are each independently selected from hydrogen; alkyl; alkoxy; hydroxy; halogen; trifluoromethyl; cyano; nitro; amino; alkylamino, NHCOR^9 , CO_2R^9 , $-\text{CON}(\text{R}^9)_2$, $-\text{NHSO}_2-\text{R}^9$, $-\text{SO}_2\text{N}(\text{R}^9)_2$ wherein R^9
15 represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl or R^9 comprises a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which can be substituted by alkyl or acyl; or $(\text{R}^9)_2$ together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another
20 heteroatom which can be substituted by alkyl or acyl; aryl, phenylamino, phenoxy or heteroaryl wherein the phenyl, aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, hydroxy, alkoxy, halogen, trifluoromethyl, cyano, nitro, amino, NHCOR^9 , CO_2R^9 , $-\text{CON}(\text{R}^9)_2$, $-\text{NHSO}_2-\text{R}^9$, $-\text{SO}_2\text{N}(\text{R}^9)_2$ wherein R^9 is as defined above; or R^3 and R^4 or R^4 and R^5 together form a 4-8 membered saturated
25 or unsaturated ring and the other substituents R^1 , R^2 , R^3 , R^4 and R^5 is as defined above;

Y represents





wherein R^0 and R^{00} independently represents hydrogen or lower alkyl;

X represents O or S;

R^6 is hydrogen, or alkyl;

- 5 R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen; alkyl; alkoxy; hydroxy; halogen; trifluoromethyl; cyano; nitro; amino; alkylamino; $-\text{COOR}^7$; $-\text{NHSO}_2\text{-alkyl}$; $-\text{SO}_2\text{N(R}^7)_2$; $-\text{SO}_2\text{OR}^7$; $-\text{CO-R}^7$; aryl, phenylamino, phenoxy or heteroaryl wherein the phenyl, aryl or heteroaryl group may be substituted one or more times with
- 10 substituents selected from alkyl, hydroxy, alkoxy, halogen, trifluoromethyl, cyano, nitro, amino and alkylamino, $-\text{COOR}^7$; $\text{CON(R}^7)_2$; $-\text{NHSO}_2\text{-R}^7$; $-\text{SO}_2\text{N(R}^7)_2$; $-\text{SO}_2\text{OR}^7$; $-\text{CO-R}^7$, or one of R^{11} and R^{12} , R^{12} and R^{13} , R^{13} and R^{14} and R^{14} and R^{15} together form a 4-8 membered saturated or unsaturated ring and the other substituents R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above and wherein R^7 represents hydrogen, alkyl, cycloalkyl,
- 15 cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl or R^7 comprises a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms which can be substituted by alkyl or acyl; or $(R^7)_2$ together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom which can be
- 20 substituted by alkyl or acyl;

2. A compound according to claim 1 wherein one of R^1 , R^2 and R^3 is 3-hydroxy-4-oxo-pyranyl, 2-hydroxy-4-oxo-pyrimidyl, 3,5-dioxo-1,2,4-oxadiazolidinyl, 2,4-dioxo-imidazolidinyl, 2,5-dioxo-3-hydroxy-pyrrolyl, 2,5-dioxo-pyrrolidinyl, 2,4-dioxo-
- 25 1,3-thiazolidinyl, 3-hydroxy-isoxazolyl, 5-hydroxy-isoxazolyl, 3-hydroxy-isothiazolyl, 3-hydroxy-1,2,5-thiadiazolyl, tetrazolyl, 3-hydroxy-triazolyl, 3-hydroxy-pyrazolyl, 2-hydroxy-1,3,4-oxadiazolyl or 2-hydroxy-3,4-dioxo-cyclobutenyl, NH_2 , $-\text{COOR}^{16}$, $-\text{CH}_2\text{COOR}^{16}$, $-\text{CON(R}^{16})_2$, $-\text{NHSO}_2\text{-R}^{16}$, $-\text{SO}_2\text{N(R}^{16})_2$, $-\text{SO}_2\text{OR}^{16}$, $-\text{PO}_3\text{H}_2$, $-\text{PO}_3\text{RH}$, $-\text{PO}_2\text{NH}_2$, $-\text{CONHOH}$, $-\text{CONHCN}$, $-\text{CONHSO}_2\text{R}^{16}$ and $-\text{CONHNH}_2$, wherein R^{16} is
- 30 hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl or R^{16} comprises a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms which can be substituted by alkyl or acyl; or $(R^{16})_2$ together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom



which can be substituted by alkyl or acyl; and the other of R^1 , R^2 and R^3 is as defined in claim 1;

3. A compound according to any of the claims 1-2 wherein one of R^1 , R^2 and R^3 represents COOH , $\text{CH}_2\text{COOR}^{16}$, $\text{CON}(\text{R}^{16})_2$, tetrazolyl, methyltetrazolyl, $\text{NHSO}_2\text{R}^{16}$, CO_2R^{16} , $\text{CO}_2\text{N}(\text{R}^{16})_2$, $\text{SO}_2\text{N}(\text{R}^{16})_2$, $\text{CONHSO}_2\text{R}^{16}$, $\text{SO}_2\text{OR}^{16}$, wherein R^{16} is as defined in claim 2;

4. A compound according to any of the claims 1-3 wherein R^4 , R^5 and the remaining of R^1 , R^2 or R^3 independently represents hydrogen, alkyl, nitro, amino, alkylamino, CO_2R^9 , CF_3 , alkyl, halogen, hydroxy, alkoxy, NHCOR^9 , $-\text{CON}(\text{R}^9)_2$, aryl optionally substituted with NO_2 , $\text{CON}(\text{R}^9)_2$, NHCOR^9 , $\text{SO}_2\text{N}(\text{R}^9)_2$, CO_2R^9 , wherein R^9 is as defined in claim 1;

5. A compound according to any of the claims 1-4 wherein one or more of R^{11} , R^{12} , R^{13} , R^{14} and R^{15} independently represents CF_3 , halogen, alkyl, alkoxy, NO_2 , acyl, COOH , $\text{CH}_2\text{COOR}^{16}$, $\text{CON}(\text{R}^{16})_2$, $\text{NHSO}_2\text{R}^{16}$, CO_2R^{16} , $\text{CO}_2\text{N}(\text{R}^{16})_2$, $\text{SO}_2\text{N}(\text{R}^{16})_2$, $\text{CONHSO}_2\text{R}^{16}$, $\text{SO}_2\text{OR}^{16}$ or aryl optionally substituted with NHCOR^7 , CO_2R^7 , $-\text{CON}(\text{R}^7)_2$, $-\text{NHSO}_2\text{R}^7$, $-\text{SO}_2\text{N}(\text{R}^7)_2$ wherein R^7 is as defined in claim 1; or R^{11} and R^{12} together with the phenyl group to which they are attached forms a 6-membered unsaturated ring;

6. A compound according to any of the claims 1-5, said compound being N-phenyl-N'-(2-carboxyphenyl) urea;

25 N-(3-trifluoromethylphenyl)-N'-(2-carboxyphenyl)-N'-methyl urea;

N-(3-trifluoromethylphenyl)-N'-(4-bromo-2-carboxyphenyl) urea;

N-(3-trifluoromethylphenyl)-N'-(2-carboxy-4-chlorophenyl) urea;

N-(3-trifluoromethylphenyl)-N'-(2-carboxy-4-fluorophenyl) urea;

3-trifluoromethylphenyl-2-phenyl urea;

30 N-(3-bromophenyl)-N'-(2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-trifluoromethylphenyl)-N'-(4'-(N,N-dimethylsulfamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-bromophenyl)-N'-(4'-(N,N-dimethylsulfamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;

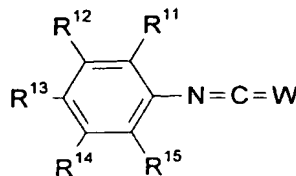


- N-(3-bromophenyl)-N'-(4'-(N,N-dimethylcarbamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4-amino-2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4-acetylamino-2-(1-H-tetrazol-5-yl)phenyl) urea;
- 5 N-(3-trifluoromethylphenyl)-N'-(4'-carbamoyl-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4'-(N,N-dimethylcarbamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;
- N'-(3-trifluoromethylphenyl)-N'-(4'-carboxy-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea;
- N-(3-trifluoromethylphenyl)-N'-(4'-(N-phenylcarbamoyl)-2-(5-tetrazoyl)-4-biphenyl)
- 10 urea;
- N-(2-indan)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(4-biphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-biphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-acetylphenyl)-N'-(2-(1-H-tetrazol-5-yl)phenyl) urea;
- 15 N-(3-trifluoromethylphenyl)-N'-(2-(1-methyltetrazol-5-yl)-4-biphenyl) urea;
- N-(3-biphenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-(3-pyridyl)phenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea;
- N-(3-bromophenyl)-N'-(4-bromo-2-(1-H-tetrazol-5-yl)phenyl) urea;
- 1-(3-trifluoromethylphenyl)-3-(2-carboxyphenyl)-2-imidazolidone;
- 20 3-trifluoromethylphenyl-4-(4-benzoylcarbonylphenyl)-2-(1-H-tetrazol-5-yl)phenyl urea;
- 4-biphenyl-2-(1-H-tetrazol-5-yl)phenyl urea;
- N-(3-Bromophenyl)-N'-[3'-nitro-2-(1-H-tetrazol-5-yl)biphenyl] urea;
- N-(3-Bromophenyl)-N'-[4'-(sulfoamido-N-methylpiperazinium chloride)-2-(1-H-tetrazol-5-yl)-4-biphenyl] urea;
- 25 N-(3-Bromophenyl)-N'-[4'-carbamoyl-N-methylpiperazine)-2-(1-H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Dichlorophenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea;
- N-(4-Trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(4-Bromophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- 30 N-(3-Methoxyphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(3-Chlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(3-Methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
- N-(3,4-Dichlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;



- N-(2-Naphthyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-Methyl-3-nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-Chloro-4-trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(3,5-Di(trifluoromethyl)phenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
5 N-(3,5-Dimethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-Ethoxyphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-Methoxyphenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea;
N-(2-Trifluoromethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-Bromophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
10 N-(2-Chlorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-Fluorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-Chloro-3-trifluoromethylphenyl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)phenyl] urea;
N-(3-Bromophenyl)-N'-(2,3-difluorophenyl) urea;
N-(2-Methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
15 N-(2-Ethylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(4-Methylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(2-Nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-(3-Fluorophenyl)-N'-[4-bromo-2-(1-H-tetrazol-yl)phenyl] urea;
N-(4-[2-Propyl]phenyl)-N'-[4-bromo-2-(1-H-tetrazol-5yl)phenyl] urea;
20 N-(3-Nitrophenyl)-N'-[4-bromo-2-(5-tetrazol-5-yl)phenyl] urea;
N-(3-Acetylphenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea; or
N-(4-Nitrophenyl)-N'-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
and pharmaceutically acceptable addition salts of any of the compounds above;

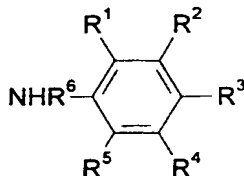
- 25 7. A method for the preparation of a compound of any of the claims 1-6,
comprising:
a) reacting a compound having the formula





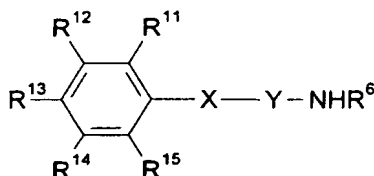
37

wherein W is O, or S and R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above, with a compound having the formula



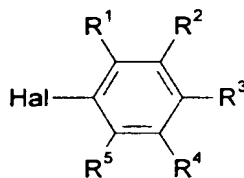
5 wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 is as defined above, or

b) reacting a compound having the formula



10

wherein X, Y, R^6 , R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above, with a compound having the formula



15 wherein Hal is halogen and R^1 , R^2 , R^3 , R^4 and R^5 is as defined above,

whereafter optionally the compound obtained is converted to another compound of the invention and/or a pharmaceutically acceptable salt thereof is formed using conventional methods;

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8. A pharmaceutical composition comprising a chloride channel blocker according to any of the claims 1-6, combined with one or more compounds known for treatment for bone metabolic disorders or pharmaceutically acceptable salt of these compounds, together with at least one pharmaceutically acceptable carrier or diluent.

25



9. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of the claims 1-6 or a pharmaceutically acceptable salt thereof together with at least one pharmaceutically acceptable carrier or diluent;
- 5 10. The use of a compound according to any of the claims 1-6, for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels;
- 10 11. The use of a compound according to any of the claims 1-6, for the preparation of a medicament for the treatment of sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhea, hypertension (diuretic), bone metabolic disorders, osteoclast associated disorders, bone metastasizing cancers, glaucoma, allergic or inflammatory conditions or healing ulcers;
- 15 12. The use of a compound according to any of the claims 1-6 combined with the use of other bone metabolism controlling compounds for the treatment of bone metabolic disorders or conditions;
- 20 13. A method for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels, comprising administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any of the claims 1-6;
- 25 14. A method for the treatment of a disorder or disease of a living animal body which disorder or disease is sickle-cell anaemia, brain oedema following ischaemia or tumours, diarrhea, hypertension (diuretic), bone metabolic disorders, osteoclast associated disorders, bone metastasizing cancer, glaucoma, allergic or inflammatory conditions or ulcers, comprising administering to such a living animal body, including a
30 human, in need thereof a therapeutically effective amount of a compound of any of the claims 1-6;
15. A method for the treatment of a disorder or disease of a living animal body which disorder or disease is a bone metabolic disorder comprising administering to
35 such a living animal body, including a human, in need thereof a therapeutically

effective amount of a or more compounds according to any of the claims 1-6,
optionally in combination with a therapeutically effective amount of one or more
compounds known for treatment for bone metabolic disorders;

INTERNATIONAL SEARCH REPORT

In national Application No
PCT/DK 99/00575

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C275/42 C07C275/32 C07C381/06 C07C233/64 A61K31/17
A61K31/18 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 47 096 A (REHAU AG) 4 July 1996 (1996-07-04) example 1	1
X	EP 0 028 099 A (EASTMAN KODAK COMPANY) 6 May 1981 (1981-05-06) claim 1	1
X	EP 0 022 958 A (BAYER AG) 28 January 1981 (1981-01-28) claim 1	1, 9
X	FR 2 100 943 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 24 March 1972 (1972-03-24) claims 1,3,6	1, 7, 9
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principles or theory underlying the invention

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Int. Search Application No.

PCT/DK 99/00575

C. (Conclusion) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 290 235 A (H.H. HAUGH) 20 December 1995 (1995-12-20) claims 1,5	1,11
X	GB 1 055 786 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 18 January 1967 (1967-01-18) claims 1,10	1,7
P,X	HO 99 32463 A (BAYER CORPORATION) 1 July 1999 (1999-07-01) claims 14,15,21	1,9
X	HO 97 45400 A (NEUROSEARCH A/S) 4 December 1997 (1997-12-04) claims 1,4,8	1,7,8
X	HO 96 25157 A (SMITHKLINE BEECHAM CORPORATION) 22 August 1996 (1996-08-22) claims 9,14,15,18	1,7,9
X	HO 94 22807 A (NEUROSEARCH A/S) 13 October 1994 (1994-10-13) claims 1,3,11	1,7,9
X	HO 89 12622 A (I. LALEZARI ET AL) 28 December 1989 (1989-12-28) claims 15,22	1,9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Appl. No.

PCT/DK 99/00575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4447096 A	04-07-1996	NONE	
EP 28099 A	06-05-1981	CA 1156250 A JP 1147623 C JP 56065134 A JP 57037857 B US 4333999 A US T101601 I US B101601 I	01-11-1983 26-05-1983 02-06-1981 12-08-1982 08-06-1982 02-03-1982 02-03-1982
EP 22958 A	28-01-1981	DE 2928485 A AU 544252 B AU 6019480 A DK 302480 A EP 0049538 A ES 493327 A JP 56016411 A NO 801965 A, B, US 4405644 A ZA 8004180 A	29-01-1981 23-05-1985 15-01-1981 15-01-1981 14-04-1982 16-05-1981 17-02-1981 15-01-1981 20-09-1983 29-07-1981
FR 2100943 A	24-03-1972	DE 2136961 A GB 1281437 A	27-01-1972 12-07-1972
GB 2290235 A	20-12-1995	CA 2137755 A	08-12-1995
GB 1055786 A		NL 6407857 A NL 6515458 A	13-01-1965 31-05-1966
HO 9932463 A	01-07-1999	AU 1939999 A	12-07-1999
HO 9745400 A	04-12-1997	AU 2962197 A AU 2962297 A HO 9745111 A EP 0906273 A EP 0910358 A AU 6919698 A HO 9847879 A	05-01-1998 05-01-1998 04-12-1997 07-04-1999 28-04-1999 13-11-1998 29-10-1998
HO 9625157 A	22-08-1996	EP 0809492 A JP 11503110 T NO 983737 A US 5886044 A US 5780483 A	03-12-1997 23-03-1999 14-10-1998 23-03-1999 14-07-1998
HO 9422807 A	13-10-1994	AT 175955 T AU 683654 B AU 6537894 A CA 2160128 A DE 69416119 D DE 69416119 T EP 0693053 A FI 954746 A JP 8510448 T NO 953956 A NZ 265052 A US 5696138 A	15-02-1999 20-11-1997 24-10-1994 13-10-1994 04-03-1999 27-05-1999 24-01-1996 17-11-1995 05-11-1996 07-12-1995 19-12-1997 09-12-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Application No.

PCT/DK 99/00575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8912622 A	28-12-1989	US 4921997 A	01-05-1990
		EP 0420930 A	10-04-1991
		JP 3505728 T	12-12-1991
		US 5472981 A	05-12-1995
		US 5093367 A	03-03-1992
		US 5292935 A	08-03-1994